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Technical Report Series
No. 458

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BUTYL BENZYL PHTHALATE (CAS NO. 85-68-7) IN F344/N RATS (FEED STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF BUTYL BENZYL PHTHALATE

(CAS NO. 85-68-7)

IN F344/N RATS

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
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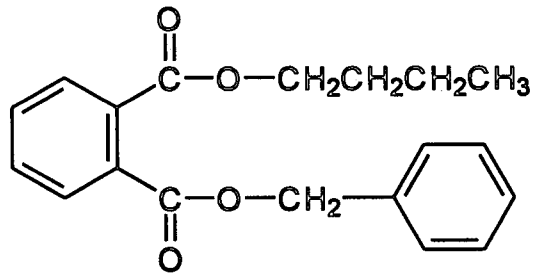
ABSTRACT



BUTYL BENZYL PHTHALATE

CAS No. 85-68-7

Chemical Formula: $C_{19}H_{20}O_4$ Molecular Weight: 312.39

Synonyms: A13-14777; BBP; 1,2-benzenedicarboxylic acid butyl phenylmethyl ester (9CI); benzyl *n*-butyl phthalate; *n*-butyl benzyl phthalate; butyl phenylmethyl 1,2-benzenedicarboxylate; phthalic acid benzyl butyl ester (8CI)
Trade names: Palatinol BB; Santicizer 160; Sicol 160; Unimoll BB

Butyl benzyl phthalate is a plasticizer added to polymers to give flexibility and softness. It is used extensively in polyvinyl chloride and in cellulose plastics, polyvinyl acetate, polysulfides, and polyurethane. Butyl benzyl phthalate was nominated as part of a class study of phthalates. Previous studies of butyl benzyl phthalate by the NTP (1982a) resulted in chemical-related mortality in male rats beginning at about 14 weeks of exposure and, thus, were inadequate for evaluating carcinogenicity in male rats. The companion studies revealed a marginal increase in leukemia in female rats and no evidence of carcinogenicity in B6C3F$_1$ mice. Consequently, the present evaluations were conducted only in F344/N rats. Male and female F344/N rats were given butyl benzyl phthalate (at least 97% pure) in feed for 10 weeks, 26 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, mouse bone marrow cells, and *Drosophila melanogaster*.

10-Week Modified Mating Study in Rats

Groups of 15 male F344/N rats were given 0, 300, 2,800, or 25,000 ppm butyl benzyl phthalate (equivalent to average daily doses of approximately 20, 200, or 2,200 mg butyl benzyl phthalate/kg body weight) in feed for 10 weeks. All rats survived to the end of the study. The final mean body weight and body weight gain of the 25,000 ppm group were significantly less than those of the controls. Feed consumption by the 25,000 ppm group was less than that by the controls at the end of the study. A few minimal hematology changes occurred in the 25,000 ppm male rats. There was some evidence of a minimal anemia characterized by a decreased erythrocyte count and increases in mean cell hemoglobin and platelet count. The absolute and relative prostate gland weights of the 25,000 ppm males were significantly less than those of the controls. Degeneration of the seminiferous

tubule germinal epithelium was observed in all males from the 25,000 ppm group. The absolute right cauda, right epididymis, and right testis weights of the 25,000 ppm males were significantly less than those of the controls. The epididymal spermatozoal concentrations in 2,800 and 25,000 ppm males were significantly less than that in the controls. Although 10 females mated to 25,000 ppm males were initially found to be sperm positive, none of these females were pregnant at necropsy. The fertility indices of males and females in the 25,000 ppm group were significantly lower than those of the controls. The maternal body weights of females mated to 300 and 2,800 ppm males were similar to those of females mated to control males. There were no significant differences in litter data between the controls and the 300 and 2,800 ppm groups.

26-Week Study in Rats

Groups of 15 male F344/N rats were given 0, 300, 900, 2,800, 8,300, or 25,000 ppm butyl benzyl phthalate in feed for 26 weeks. Dietary levels of 300, 900, 2,800, and 8,300 ppm delivered average daily doses of approximately 30, 60, 180, and 550 mg butyl benzyl phthalate/kg body weight. The final mean body weight and body weight gain of the 25,000 ppm males were significantly less than those of the controls. Except for the 25,000 ppm males, feed consumption by all exposed groups was similar to that by the controls. An exposure-related macrocytic responsive anemia was present in the 25,000 ppm group at all time points. Additionally, minimal erythrocyte count decreases occurred sporadically in the 2,800 and 8,300 ppm groups at various time points. Reticulocyte counts were increased on days 60 and 90. Increases in mean cell hemoglobin and mean cell hemoglobin concentrations occurred in the 8,300 and 25,000 ppm rats. The absolute right cauda, right epididymis, and right testis weights and the sperm concentration of 25,000 ppm males were significantly less than those of the controls. The incidences of hypospermia and of atrophy of the seminiferous tubule in the testis and of hypospermia in the epididymis in 25,000 ppm males were significantly greater than those in the controls. Degenerative changes of the testis and epididymis in the 25,000 ppm males were qualitatively and quantitatively similar to those observed in males in the 10-week modified mating study.

2-Year Study in Rats

Groups of 60 male F344/N rats were given 0, 3,000, 6,000, or 12,000 ppm butyl benzyl phthalate (equivalent to average daily doses of approximately 120, 240, or 500 mg butyl benzyl phthalate/kg body weight), and groups of 60 female F344/N rats were given 0, 6,000, 12,000, or 24,000 ppm butyl benzyl phthalate (equivalent to average daily doses of approximately 300, 600, or 1,200 mg/kg) in feed for 2 years.

Survival, Body Weights, and Feed Consumption

Survival of all exposed groups of male and female rats was similar to that of the controls. Mean body weights of the 12,000 ppm males and 24,000 ppm females were less than those of the controls throughout most of the study. Feed consumption by the females exposed to 24,000 ppm was less than that by the controls at the beginning of the study, but was similar to that by the controls by week 6.

Hematology and Hormone Assays

In general, hematology changes were sporadic and minor. At 6 months, a minimal decrease in erythrocyte count and an increase in mean cell hemoglobin, similar to that which occurred in the 26-week study, occurred in male rats in the 12,000 ppm group. In female rats, a decreased hematocrit value occurred at 15 months in the 24,000 ppm group. There was also a mild decrease in triiodothyronine concentrations in the 24,000 ppm females at 6 and 15 months and at the end of the study.

Pathology Findings

At 2 years, the incidences of pancreatic acinar cell adenoma and adenoma or carcinoma (combined) in 12,000 ppm males were significantly greater than those in the controls. The incidences of adenoma and of adenoma or carcinoma (combined) in 12,000 ppm males exceeded the ranges of historical controls from NTP 2-year feed studies. One carcinoma was observed in one 12,000 ppm male, and two adenomas were observed in 24,000 ppm females. At 2 years,

the incidence of focal hyperplasia of the pancreatic acinar cell in 12,000 ppm males was significantly greater than that in the controls.

At 2 years, transitional epithelial papillomas in the urinary bladder were observed in one control female and in two 24,000 ppm females. The incidence of this neoplasm exceeded the range of historical controls from NTP 2-year feed studies. The incidence of transitional epithelial hyperplasia in 24,000 ppm females was significantly greater than that in the controls.

The absolute right kidney weight of 12,000 ppm females and the relative right kidney weights of all exposed groups of males and of 24,000 ppm females were significantly greater than those of the controls at the 15-month interim evaluation. The severities of renal tubule pigmentation in 12,000 ppm males and in 24,000 ppm females were greater than those in the controls at 15 months and 2 years. At 2 years, the incidences of kidney mineralization in 6,000 and 24,000 ppm females were significantly less than that in the controls, and the severity was decreased in exposed females. The incidence of preputial gland adenoma or carcinoma (combined) in 12,000 ppm male rats was significantly less than in the controls, and the incidences occurred with a negative trend.

Genetic Toxicology

Results from *in vitro* mutagenicity tests with butyl benzyl phthalate were uniformly negative. No mutagenic response was obtained in any of several strains of *Salmonella typhimurium* treated with up to 11,550 μg/plate butyl benzyl phthalate, with or without S9 metabolic activation enzymes. Negative results were also obtained in *in vitro* studies of mammalian cell systems with and without S9. No induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells or sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells were observed. These assays also were conducted with and without S9.

No significant increase in sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* after administration of butyl benzyl phthalate either in feed or by injection.

In contrast to the negative results obtained *in vitro* and in *Drosophila*, butyl benzyl phthalate gave positive responses in two *in vivo* studies with mice. Results of a mouse bone marrow sister chromatid exchange test were positive at sample times of 23 and 42 hours, but no confirmatory test was conducted. Chromosomal aberrations were induced in bone marrow cells of male mice sampled 17 hours after intraperitoneal injection of 5,000 mg/kg butyl benzyl phthalate.

Conclusions

Under the conditions of this 2-year feed study, there was *some evidence of carcinogenic activity** of butyl benzyl phthalate in male F344/N rats based on the increased incidences of pancreatic acinar cell adenoma and of acinar cell adenoma or carcinoma (combined). There was *equivocal evidence of carcinogenic activity* of butyl benzyl phthalate in female 344/N rats based on the marginally increased incidences of pancreatic acinar cell adenoma and of transitional epithelial papilloma of the urinary bladder.

Exposure of rats to butyl benzyl phthalate in feed for 2 years resulted in focal hyperplasia in the pancreas in male rats and in transitional epithelial hyperplasia in the urinary bladder of female rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Butyl Benzyl Phthalate

	Male F344/N Rats	Female F344/N Rats
Doses	0, 3,000, 6,000, or 12,000 ppm in feed	0, 6,000, 12,000, or 24,000 ppm in feed
Body weights	12,000 ppm group less than control group	24,000 ppm group less than control group
2-Year survival rates	28/50, 20/50, 22/50, 22/50	25/50, 29/50, 29/50, 29/50
Nonneoplastic effects	Pancreas: focal hyperplasia (4/50, 7/49, 9/50, 12/50)	Urinary bladder: transitional epithelial hyperplasia (4/50, 0/50, 1/50, 10/50)
Neoplastic effects	Pancreas: acinar cell adenoma (3/50, 2/49, 3/50, 10/50); acinar cell adenoma or carcinoma (3/50, 2/49, 3/50, 11/50)	None
Uncertain findings	None	Pancreas: acinar cell adenoma (0/50, 0/50, 0/50, 2/50) Urinary bladder: transitional epithelial papilloma (1/50, 0/50, 0/50, 2/50)
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence
Genetic toxicology		
Salmonella typhimurium gene mutations:		Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9
L5178Y Mouse lymphoma gene mutations:		No induction of trifluorothymidine resistance
Sister chromatid exchanges		
Cultured Chinese hamster ovary cells *in vitro*:		Negative with and without S9
Mouse bone marrow *in vivo*:		Weakly positive at 23 and 42 hours
Chromosomal aberrations		
Cultured Chinese hamster ovary cells *in vitro*:		Negative with and without S9
Mouse bone marrow *in vivo*:		Positive at 17 hours; negative at 36 hours
Sex-linked recessive lethal mutations		
Drosophila melanogaster:		No induction of sex-linked recessive lethal mutations

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (I) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on butyl benzyl phthalate on 20 June 1995 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 20 June 1995, the draft Technical Report on the toxicology and carcinogenesis studies of butyl benzyl phthalate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. F.W. Kari, NIEHS, introduced the toxicology and carcinogenesis studies of butyl benzyl phthalate by describing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplastic lesions in male rats and uncertain neoplastic findings in female rats as well as chemical-related nonneoplastic lesions in male and female rats. Dr. Kari noted that there had been an earlier 2-year NTP study with butyl benzyl phthalate in which there was no evidence of adverse effects in mice and a marginally increased incidence of mononuclear cell leukemia in female rats. This study was inadequate in male rats due to high mortality beginning around week 14. Thus, the design of the subchronic phase of the current study in male rats was more elaborate in an attempt to determine if early mortality would be a problem. The design included a 10-week modified mating trial as well as other indices of reproductive toxicity. The proposed conclusions for the 2-year study were *some evidence of carcinogenic activity* in male F344/N rats and *equivocal evidence of carcinogenic activity* in female F344/N rats.

Dr. Reddy, a principal reviewer, agreed with the proposed conclusions although he thought that the proposed conclusions from the previous 2-year study in mice should be cited. Dr. Kari responded that this information would be added to the Abstract. Dr. Reddy noted the 20% incidence of pancreatic acinar cell adenoma versus only a 2% incidence of carcinoma in 12,000 ppm male rats. He asked for definition of the criteria for distinguishing adenomas from carcinomas since, based on his experience, he wondered if carcinomas were underrepresented. Dr. J.R. Hailey, NIEHS, said more would be added concerning how the distinction was made between adenomas and carcinomas (p. 43). While metastasis was an easy marker for a carcinoma, other features were used such as cellular pleomorphism or tremendous heterogeneity in the growth pattern, cellular atypia, and high mitotic index.

Dr. Klaassen, the second principal reviewer, agreed with the proposed conclusions. He said that reference to the mouse studies should be made earlier in the Technical Report, preferably in the Abstract, and that more information should be included on phthalate carcinogenicity in regard to the rationale (p. 20). Because of the known effects of phthalates on male reproduction, Dr. Klaassen was pleased to see reproduction studies in this Technical Report.

Dr. Ryan, the third principal reviewer, agreed with the proposed conclusions. She wondered whether there should also be a conclusion regarding the reproductive toxicity. Dr. Ryan found it worrisome that so many animals died in the 26-week study during anesthesia prior to blood sampling and asked whether there was any bias here whereby weaker or sicker animals were more likely to die during the procedure. Dr. Kari said he could only speculate that the higher ratio of carbon dioxide to oxygen than generally used may have contributed to the excessive mortality. It did not appear to be due to chemical interaction, because the numbers of deaths in control animals were similar to those in exposed groups of animals.

Dr. Miller noted the National Institute for Occupational Safety and Health (NIOSH) reference that over 300,000 workers were potentially exposed to butyl benzyl phthalate and asked whether there were data about occupational exposure in terms of airborne concentrations. Dr. J. Haartz, NIOSH, commented that their database does not have such quantitative information. She reported that the Occupational Safety and Health Administration does not have an exposure database and offered to follow up on that for Dr. Kari.

Dr. M. Stevens, Manager of Toxicology Projects, Monsanto Business Services, stated that the biggest

concern of the Monsanto Company, a primary maker of butyl benzyl phthalate, was that this study not be considered in isolation from theirs and studies of others. He pointed out that survival and neoplasm findings in the earlier NTP study were not repeated in the current study, and, further, when diet restriction was employed, the increased incidences of pancreatic neoplasms seen in the current study were eliminated. Thus, looking at the multiple studies with no consistent reported findings, Dr. Stevens thought a decision could not be made about the potential carcinogenicity of butyl benzyl phthalate.

Dr. Miller asked the industry representatives for information on occupational and consumer exposures. Dr. R. Hogue, Monsanto Company, said occupational exposure is quite low, as is consumer exposure in vinyl flooring, because the butyl benzyl phthalate is bound into a polymeric system. He said exposure data would be provided to the NTP. Dr. R.W. Hart, NCTR, returned to the effects of feed restriction on neoplasm incidence, noting that in 30-month feed restriction male rats, three exposed rats developed pancreatic acinar cell adenomas. In feed-restricted exposed females at 30 months, there was a statistically significant increased incidence of neoplasms of the urinary bladder.

Dr. Ryan moved that the Technical Report on butyl benzyl phthalate be accepted with the revisions discussed and with the conclusions as written for male rats, *some evidence of carcinogenic activity*, and for female rats, *equivocal evidence of carcinogenic activity*. Dr. Reddy seconded the motion, which was accepted unanimously with 10 votes.